LIVER TRANSPLANTATION IN METHYLMALONIC AND PROPIONIC ACIDEMIA

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LIVER TRANSPLANT

• Describe propionic and methylmalonic acidemia
• Understand current treatment of organic acidemias
• Liver transplant in organic acidemias

The presenter has no conflict of interest to disclose for this presentation.
PROPIONIC ACIDEMIA

Autosomal recessive organic acidemia

Cause: defective propionyl-CoA carboxylase, composed of two non-identical subunits (α and β) encoded by two separate genes (PCCA on 13q32 and PCCB on 3q21-22) any of which can be impaired.

• This enzyme requires biotin and can also be defective in holocarboxylase synthase deficiency and biotinidase deficiency, enzymes needed for the insertion or recycling of biotin. Biotin binds to the α subunit of propionyl CoA carboxylase and is essential for enzyme stability and activity.

Pathogenesis: toxicity of propionic acid, metabolic acidosis, hyperammonemia, and ketonuria; defective energy production due to depletion of intermediates of the Krebs cycle, carnitine depletion.
METHYLMALONIC ACIDEMIA

- Similar in most aspects to propionic acidemia.
- Cause: defect in methyl malonyl CoA mutase or in adenosyl B12 synthesis (majority defect in B12 metabolism)
- Associated or not to homocystinuria
- Rare form due to racemase deficiency
Propionyl CoA + CO$_2$ + ATP = Succinyl CoA + ADP
The metabolism of propionic acid occurs inside mitochondria. Succinyl CoA produced in the reaction can directly flow to the citrate cycle to produce energy.
CLINICAL PRESENTATION

• 1. Classic: Refusal of feeding, vomiting (so severe to suggest pyloric stenosis), tachipnea, lethargy progressing to coma 18-96 h after birth.
• 2. Failure to thrive with only mild acidosis
• 3. Neurological presentation without ketosis (severe hypotonia, delays, seizures)
PHYSICAL EXAMINATION

• Shock, severe hypotonia (in propionic acidemia), hypertonia (in MMA).
• Many patients with propionic acidemia acquire characteristic facial features with frontal bossing, depressed nasal bridge, long phyltrum, upward curvature of the lips.
DIAGNOSIS

Clinical presentation, labs: metabolic acidosis, hyperammonemia, ketonuria, thrombocytopenia, neutropenia

**Urine organic acids**: Methylcitric acid (others: 3-OH-propionic, propionylglycine, tiglylglycine)

Methylmalonic acid in MMA.

**Plasma acylcarnitine profile**: C3-carnitine (low free carnitine); Plasma amino acids usually show severe hyperglycinemia (600-1,200 mM) in patients beyond the neonatal period.

**Confirmation**: Enzyme assay in WBC (PPA), DNA testing (2 genes for PPA), gene panel for MMA
Propionic acidemia: neonatal presentation
Propionic acidemia: late presentation

- 3-OH Propionic Acid
- Methylcitric Acid
METHYLMALONIC ACIDEMIA

Methylmalonic Acid
NEWBORN SCREENING

• These disorders are identified by universal newborn screening by MS/MS: elevated C3 (propionyl) carnitine

• Many patients, however, are symptomatic or very sick by the time the newborn screening results are back.
TREATMENT

• Treatment of the acute attack should start even before a definitive diagnosis is established: IVF with glucose/intralipids/insulin.
• Carnitine administration
• Dialysis if needed
• Metronidazole to suppress propionic acid production by the gut
• Chronic treatment consists of low protein diet with special formula lacking threonine, valine, isoleucine, methionine, odd-chain fatty acids
• Carnitine supplements
50% of propionate derives from protein (valine, methionine, isoleucine, threonine; VOMIT), 25% from odd chain fatty acids and cholesterol, 25% from the metabolism of pyruvate of bacteria in the gut.

Catabolism of the nucleotides Thymine and Uracil also produces propionate.

COMPLICATIONS

- Pancreatitis
- Osteoporosis in older children
- Hypotonia may progress to hypertonia and dystonia
- Metabolic stroke
- Cardiomyopathy
- Frequent infections (reported in Saudi Arabia for PPA)
- Progressive kidney failure

COMPLICATIONS CAN OCCUR EVEN WITH OPTIMAL THERAPY
LIVER TRANSPLANT IN METHYLMALONIC AND PROPIONIC ACIDEMIA

• The enzymes defective in these conditions are expressed in most organs and tissues of the body.
• Liver transplant replaces one of the major organs, but not all of them.
• Liver transplant is not a cure.
Liver transplantation for PA (N=20). *PCC activity of skin fibroblasts nmol/min/mg (controls, 0.1-0.9). Ref, reference; LDLT, Living Donor Liver Transplantation; LR, living related; ALT, auxiliary liver transplantation; PMC, poor metabolic control; CMP, cardiomyopathy; NS, neurologic symptoms; FH, family history; Neo, neonatal

LIVER TRANSPLANT IN PROPIONIC ACIDEMIA

### Table 1: Clinical characteristics of the patients before and after transplantation

<table>
<thead>
<tr>
<th>Patient number</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Center</strong></td>
<td>BCH</td>
<td>NIC</td>
<td>NIC</td>
<td>BCH</td>
<td>BCH</td>
<td>BCH</td>
<td>BCH</td>
<td>BCH</td>
<td>BCH</td>
<td>NIC</td>
<td>NIC</td>
<td>NIC</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>F</td>
</tr>
<tr>
<td><strong>Age at LT</strong></td>
<td>2.2</td>
<td>7.1</td>
<td>9.0</td>
<td>1.2</td>
<td>1.1</td>
<td>2.4</td>
<td>1.1</td>
<td>1.7</td>
<td>3.9</td>
<td>6.7</td>
<td>6.5</td>
<td>6.3</td>
</tr>
<tr>
<td><strong>Indication for LT</strong></td>
<td>Decompensation</td>
<td>Decompensation</td>
<td>Decompensation</td>
<td>Pressurized treatment</td>
<td>Decompensation</td>
<td>Decompensation</td>
<td>Decompensation</td>
<td>Decompensation</td>
<td>Decompensation</td>
<td>Cardiomyopathy</td>
<td>Decompensation</td>
<td>Decompensation</td>
</tr>
<tr>
<td><strong>Graft type</strong></td>
<td>1st and 2nd LT: Left split liver</td>
<td>Whole liver</td>
<td>Whole liver</td>
<td>Whole liver</td>
<td>Whole liver</td>
<td>Right split liver</td>
<td>1st LT: Whole liver; 2nd and 3rd LT: Left split liver</td>
<td>1st LT: Left split liver; 2nd LT: Left split liver</td>
<td>Left split liver</td>
<td>1st and 2nd LT: Right split liver</td>
<td>Left split liver</td>
<td>Whole liver</td>
</tr>
<tr>
<td><strong>Average number of decompensations per year</strong></td>
<td>3</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>6</td>
<td>NA</td>
<td>NA</td>
<td>8</td>
<td>5</td>
<td>4</td>
<td>24</td>
</tr>
<tr>
<td><strong>Perioperative complications</strong></td>
<td>1st LT: Primary nonfunction; Renal transplantation D0; 2nd LT: Heart failure D0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Primary nonfunction</td>
<td>1st LT: HAT D1 &amp; bilater al septic D4; 2nd LT: HAT D0; 3rd LT: 0</td>
<td>Primary nonfunction</td>
<td>1st LT: HAT; hepatic dysfunction and ARDS D2; 2nd LT: HAT</td>
<td>Heart failure D14</td>
<td>1st LT: ARDS and HAT D2; 2nd LT: ARDS D7</td>
<td>Heart failure D0</td>
</tr>
<tr>
<td><strong>GFR before LT</strong></td>
<td>NA</td>
<td>NA</td>
<td>81</td>
<td>NA</td>
<td>69</td>
<td>91</td>
<td>91</td>
<td>70; 3 years after LT</td>
<td>NA</td>
<td>90</td>
<td>122</td>
<td>80</td>
</tr>
<tr>
<td><strong>GFR after LT</strong></td>
<td>NA</td>
<td>NA</td>
<td>69</td>
<td>69</td>
<td>91</td>
<td>116</td>
<td>75</td>
<td>77; 35 years after LT</td>
<td>NA</td>
<td>90</td>
<td>122</td>
<td>80</td>
</tr>
<tr>
<td><strong>Long term complications (year after LT)</strong></td>
<td>Death D7 by multiorgan failure</td>
<td>Death D22 by hepatic failure</td>
<td>21 years</td>
<td>21 years</td>
<td>Death D2 by hepatic failure</td>
<td>17 years</td>
<td>Death D3 by hepatic failure</td>
<td>Death D14 by multiorgan failure</td>
<td>Death D20 by multiorgan failure</td>
<td>8 years</td>
<td>Death D12 by multiorgan failure</td>
<td>1 year</td>
</tr>
</tbody>
</table>

**Notes:**
- **BCH:** Birmingham Children’s Hospital
- **NIC:** Nicholas G. Kidd Hospital
- **HAT:** Hepatic artery thrombosis
- **ARDS:** Acute respiratory distress syndrome
- **PTLD:** Posttransplant lymphoproliferative disorder
- **GFR:** Glomerular filtration rate (mL/min/1.73 m²)

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**References:**
- Charbit-Henrion F, Lacaille P, McKiernan et al.
- Sharif K, Chardot C, Hubert P, Dupic L

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**Title:** Early and Late Complications After Liver Transplantation for Propionic Acidemia in Children: A Two Centers Study
LIVER TRANSPLANT IN PROPIONIC ACIDEMIA

Complications

11/32 patients deceased after the transplant (34%), most of them within a few months from the transplant and most of them >5 years ago.

Complications: hepatic artery thrombosis, graft failure, graft rejection, acute respiratory distress syndrome, heart failure, renal dysfunction.

Renal failure was present in half of the patients before liver and worsened in all of them.

Careful assessment of cardiac and renal functions before and after transplant, use of renal sparing immunosuppressive protocols.
LIVER TRANSPLANT IN PROPIONIC ACIDEMIA

Benefits

Improved quality of life:
Acute metabolic decompensations are abolished.
The dietary protein restriction can be significantly relaxed or abandoned.
The developmental delay seemed to stabilize.
LIVER TRANSPLANT IN PROPIONIC ACIDEMIA

Our experience

We follow 7 patients with propionic acidemia at our center, one in Nevada and one long distance. 3 had liver transplant, one had a kidney transplant in her 40s.
<table>
<thead>
<tr>
<th>Transplant Age</th>
<th>Sex</th>
<th>Post Transplant</th>
<th>Current status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 13 y F</td>
<td></td>
<td>9 m (0.76 y)</td>
<td>Liberalized diet, eats by mouth (had G-tube), no decompensations. Has type 1 diabetes. Catching up on growth and development</td>
</tr>
<tr>
<td>2 8 m M</td>
<td></td>
<td>3 y</td>
<td>Liberalized diet, normal growth, had abnormalities in basal ganglia and abnormal movement that disappeared after transplant, walks, mild hypotonia, speech delay (10-20 words)</td>
</tr>
<tr>
<td>3 3 y M</td>
<td></td>
<td>1.42 y</td>
<td>Liberalized diet, normal growth, started looking around 2 days after the transplant, very hypotonic, walks with assistance, 10-20 words</td>
</tr>
</tbody>
</table>
BIOCHEMICAL CHANGES WITH LIVER TRANSPLANT IN PPA

Decreased C3 (propionyl) carnitine levels by about one half
Free carnitine increases a little
BIOCHEMICAL CHANGES WITH LIVER TRANSPLANT IN PPA

Total carnitine decreases a little due to a decrease of esterified carnitine.
BIOCHEMICAL CHANGES WITH LIVER TRANSPLANT IN PPA

The net result is a significant decline in the esterified/free carnitine ratio.

p<0.001 versus before transplant
BIOCHEMICAL CHANGES WITH LIVER TRANSPLANT IN PPA

Decreased (normalized) glycine levels

$\text{Glycine (µmol/L)}$

Before transplant

$\text{p<0.001 versus before transplant}$

$\text{Glycine (µmol/L)}$

Before transplant

AFTER

$\text{BEFORE}$
BIOCHEMICAL CHANGES WITH LIVER TRANSPLANT IN PPA

Increased (normalized) glutamine levels

Before and after liver transplant, glutamine levels showed an increase.
**BIOCHEMICAL CHANGES WITH LIVER TRANSPLANT IN PPA**

Decreased ammonia and no more acute events
HYPERAMMONEMIA

• We still do not know what causes hyperammonemonia in propionic acidemia:
  • Reduced N-acetylglutamate
  • Anaplerosis from glutamine (synthesis of ketoglutarate from glutamine and reversal of the usual cataplerosis (loss) of the Krebs cycle intermediate alpha-ketoglutarate to generate glutamine/glutamate)
Acetyl-CoA → Succinate → Succinyl-CoA → Fumarate → Malate → Oxaloacetate → Citrate → Isocitrate → α-Ketoglutarate → Glutamate → Aspartate → Glutamine

CO₂ ATP → Propionyl-CoA → D-Methylmalonyl-CoA → L-Methylmalonyl-CoA → Succinyl-CoA → Glutamate → Aspartate → Glutamine

Propionyl-CoA carboxylase → Methylmalonyl-CoA Racemase → Methylmalonyl CoA Mutase

GLUTAMATE SYNTHASE → NH₃ → Glutamate

Aspartate (urea cycle) → Glutamine synthase → Glutamine → Glutamate → NH₃ → ATP
PLASMA AMINO ACIDS IN PROPIONIC ACIDEMIA

H.R. Filipowicz et al. / Molecular Genetics and Metabolism 88 (2006) 123–130
LIVER AND KIDNEY TRANSPLANT IN METHYLMALONIC ACIDEMIA

There is more experience worldwide with liver and/or kidney transplant in methylmalonic acidemia. This seems to be the therapy of choice in children with this condition. In the available series, most patients maintained neurodevelopmental abilities or exhibited improvements in motor skills, learning abilities, and social functioning. The liver of the patient with MMA can be used to transplant other people (without MMA) (domino transplant).

SUMMARY

• Propionic and methylmalonic acidemia are recessive disorders of the metabolism of Thr, Val, Ile, Met, odd chain fatty acids, and cholesterol
• Classic presentation is with shock, acidosis and hyperammononemia, neutropenia and thrombocytopenia
• It is diagnosed by urine organic acids (methylcitrate or methylmalonic acid), plasma amino acids (hyperglycinemia), and acyl carnitine profile (elevated C3 carnitine).
• Therapy consists in low protein diet ± a special formula low in precursor amino acids and supplemental carnitine
SUMMARY

• Patients can suffer irreversible complications with current therapy and even with optimal care there are long term complications.

• Liver transplant is not a cure, but can increase quality of life and decrease the risk of neurological decompensation in propionic and methylmalonic acidemia.

• More experience is necessary for liver transplant in propionic acidemia, while it is becoming more common in patients with severe forms of methylmalonic acidemia.
All patients with methylmalonic and propionic acidemia and their families.